## REMARKS / ARGUMENTS

By the present amendment, claim 13 has been amended in order to specify that human T cells are formed. Support for this amendment can be found throughout the application as filed, and in particular in Example 9. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants reserve the right to pursue any of the deleted subject matter in a further continuation, continuation-in-part or divisional application. The amendment does not contain new matter and its entry is respectfully requested.

The final office action dated November 13, 2007 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

**35 USC § 103**

The Examiner has rejected claims 12-13, 17, 50 and 51 under 35 USC §103 as being unpatentable over Jaleco et al. (2001, J. Exp. Med. 194:991-1001), Nakano et al. (1994, Science 265:5175), Pui et al. (Immunity, 1999, 11(3):299-308) and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754). We respectfully disagree with the Examiner for the reasons that follow.

Jaleco et al. teaches that culturing human progenitor cells with mouse S-17 stromal cells that express Delta-1 (S-17-DL1) produces low levels of CD3+ CD4+ CD8+ T-lineage cells. In fact, in Example 9 of the present application, the inventors compared their system using OP9-DL1 cells to Jaleco's system with S17-DL1 cells. The inventors observed that there is a marked difference in generation of T cells when comparing both systems. In particular, OP9 cells generated about 65% double positive cells while the S-17 DL1 cells only generated about 5% double positive cells. Therefore, based on the

very low levels of human T-lineage cells generated by Jaleco et al., one of skill in the art would not be motivated to use murine stromal cells in order to prepare mature T cells that are TCR-$\alpha\beta^+$ $CD8^+$ or TCR-$\gamma\delta^+$ T cells as claimed in claim 12. In particular, because of a total failure to detect any mature T cells by Jaleco et al, there would be no motivation to expect that if T cells were to be generated using OP9-DL1 cells that these cells would show the ability to behave like mature functional T cells, as shown in several Examples.

The deficiencies in Jaleco et al. of not generating mature T cells are not remedied in Nakano et al., Pui et al. or Tatsumi et al., either alone or in combination. Nakano et al. uses OP9 cells to grow murine B cells, and no indications are provided that this system would support maturation to a functional or late stage of lymphocyte development. Nakano et al. is not concerned with preparing mature T cells.

Pui et al. discloses that Notch 1 provides regulatory signals in early lymphopoiesis and oncogenic transformation of lymphocytes by dysregulated Notch signals. Pui does not disclose using OP9 cells transfected with DL-1 in order to induce T cell formation or provide any guidance in the use of Notch ligands.

Tatsumi et al. relates to the generation of phenotypic mature T cells from CD3- CD4- CD8- precursors. However, Tatsumi et al. does not teach using stem cells or progenitor cells to prepare mature T cells. Tatsumi also does not teach using OP-9 stromal cells, rather it instructs the reader to use thymus derived stromal elements, which would teach away from using OP9 cells, which are bone marrow derived.

Therefore, none of the cited references teach or suggest that OP9-DL cells can support mature T cell development. Jaleco et al., using different murine stromal cells, was unable to prepare mature T cells. Nakano et al. relates to a murine system. One of skill in the art would not predict that murine stromal cells could be used to generate mature T

cells based on the work of both Jaleco et al. and Nakano et al. T cell development is a complex process. The showing by Jaleco et al. that one type of murine stromal cell (S-17-DL1 cells) could be used to prepare low numbers of immature T cells, would not be predictive of how OP9-DL1 cells would function. Nakano teaches that OP9 cells are useful in preparing B cells and provides no motivation to use such cells to prepare mature T cells. Therefore, based on the teachings of the prior art, it was unexpected that mature TCR-$\alpha\beta^+$ $CD8^+$ and TCR-$\gamma\delta^+$ T cells could be generated using OP9-DL1 cells.

For the Examiner's benefit, we are enclosing a review article on T-cell development (Zuniga-Pflucker, Nature Reviews, Vol. 4, Jan. 2004). The article provides a thorough yet concise summary of what was known about culture systems for T cell development prior to the present invention. In particular, it was believed that the only *in vitro* system for generating T cells was the fetal thymus organ culture (FTOC) system. It was a long held view "that T cells could not be generated from stem cells using a simple stromal cell monolayer" (see page 70, column 1). The inventors unexpectedly demonstrated that OP9-DL1 cells were able to induce the differentiation of stem cells to mature T cells. This invention is clearly advantageous over the prior art as it provides a simple yet efficient culture system that greatly facilitates the generation of T cells.

Applicant was informed by the previous Examiner that amending claim 12 to recite mature T cells would overcome the art. Applicant made such an amendment on May 15, 2007 and the rejection of claims 12-13 and 17 under 35 USC §103 as being unpatentable over Jaleco et al.; Nakano et al. and Tatsumi et al. was withdrawn in the office action dated August 8, 2007. It is an unfair delay to the Applicant for prosecution to be re-opened on the basis of an objection that was previously overcome.

In view of the foregoing, we respectfully request that the objection to claims under 35 USC §103 be withdrawn.

We note that claims 22 and 52-53 are allowable.

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, he is kindly requested to contact Micheline Gravelle at 416-957-1682 at his convenience.

Respectfully submitted,

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